DESIGN REFINEMENTS

Questions to be resolved

CONS. NUMBER	QUESTION	RECOMMENDATION	COMMENT
1 [all]	Lower limit for 'current smoker'	1 cig./ month **1-2 cig/wk – ELVES** **Exsmokers who have not smoked for at least one year are considered as nonsmokers. - TRICKER**	Reasonable distinction between non-smokers and occasional smokers (ref.?) **Smoking cessation for at least a year is not going to result in a higher biomarker level than would be expected for never smokers. – TRICKER** **Used in other studies, like IARC – KINSER** **Another approach is to have three groups:** **1. nonsmoker (includes never smokers)** **2. Smokers of less than 5 cigarettes per day who would NOT be used as subjects** **3. Smokers of 5 or more per day whom could be used as subjects.** **– LEYDEN** **Numerous studies define never-smokers as those who have smoked less than 1 cigarette per day during a one-year period. (IARC multi-center study.) Almost all ETS studies have used this definition. - SANDERS**
2 [Nelson, Roemer]	What to do with number of collected cig. butts?	Regression analysis against reported cig./day; if consistent: use for regression against all smoke constituents; if inconsistent, (difference is greater than a pre-determined magnitude) **Use to confirm that the reported cigarette brand is actually smoked.** **Measure unsmoked part of tobacco rod to calculate how much of the cigarette is normally smoked. – TRICKER** **Used to validate reported number of cigarettes smoked by individual smoker. - LEYDEN**	The collected cigarette butts can be used as relatively independent confirmation of reported information from the questionnaires (amount smoked, brand smoked, etc). – NELSON **Detection limits would make it unlikely to detect changes at lower usage than 1-2 cig./wk- ELVES** **Could this actually be an exclusionary factor—if subject is excluded from study as "unreliable"? – KINSER**

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DESIGN REFINEMENTS

CONS. NUMBER	QUESTION	RECOMMENDATION	COMMENT
3 [Tricker, Haussmann]	Use of contraceptives and hormone replacement therapy as exclusion criteria	No exclusion **Exclude pregnant women and women over 50 (i.e., post-menopausal women) - TRICKER**	No interference with biomarkers of exposure expected; exclusion would severely limit the study population. **Significant increases in prostaglandin turnover occur during pregnancy and in post-menopausal women (Fischer et al., Biochem et Biophysica Acta 876, 194-199,1986). Period of menstrual cycle may also affect prostaglandin synthesis and urinary excretion of metabolites (Rangemark and Wennmalm, Clin. Sci., 81, 11-15, 1991). – TRICKER** **Collect the information - LEYDEN**
4 [Carmines, Elves]	Should GCP compliance relate to FDA + ICH regs	Yes	***FDA's Guidance for Industry* (1996) adopts verbatim ICH GCP - ELVES** Although alternatives are possible, no reason obvious at this time **"Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible" FDA/ICH E6 Good Clinical Practice: Consolidated Guidance (1996) - ELVES**
5 [Nelson, Sanders]	Self-reporting or aided questionnaires	Aided (by trained staff; computer-supported) **Interview by trained staff using a structured questionnaire. - TRICKER**	Reduces misreporting but increases potential bias Reduce errors associated with literacy levels and comprehension. – NELSON **The questionnaire that we will use will most likely be fairly complicated. This necessitates the use of an aided questionnaire. The use of aided questionnaires is quite common in epidemiological studies on ETS. (IARC, Fontham). To reduce bias, it is necessary to properly train the interviewers. - SANDERS**

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DESIGN REFINEMENTS

CONS. NUMBER	QUESTION	RECOMMENDATION	COMMENT
6 [von Holt, Tricker]	What kind of medications should be used for exclusions?	Aspirin prophylaxis (daily doses of approx. 85 mg), chemo-therapy **Chemotherapy Acetylsalicyclic acid (ASA; aspirin) Cyclooxygenase (COX-1 and COX-2) inhibitors - TRICKER**	**Chemotherapy (subjects with cancer should be excluded) ASA use significantly reduces thromboxane metabolite excretion (Pratico et al., PNAS, 95, 3449-3454, 1998) COX-1 and COX-2 inhibitors affect arachidonic acid metabolism and hence isoprostane synthesis (Pratico et al., PNAS, 95, 3449-3454, 1998) – TRICKER** **I can understand this for biomarkers of effect/susceptibility, but not for exposure. Is there any reason to require that our initial population ALL be participating in exposure as well as susceptibility monitoring? – KINSER** **Why aspirin for all markers? - LEYDEN**
7 [von Holt, Tricker]	What kind of medications, prophylactic dietary supplementations should be reported (evaluated)?	**All current medication and OTC vitamin preparations by brand name - TRICKER** Vitamin supplementation (at least 3days/week), Regular use of herbal supplements	**Oral contraceptives and hormone replacement therapy; hypertension medications; CV conditions meds; diabetic meds, etc. - KINSER**

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DESIGN REFINEMENTS

CONS. NUMBER	QUESTION	RECOMMENDATION	COMMENT
8 [all, von Holt]	What kind of clinically manifest diseases should be excluded? • Cancer (all? Current or history?) • Diabetes • CHD • Hypertension • Arthritis • Stroke • Heart infarction • Renal dysfunctions • Bronchitis • Asthma • Hyperlipidemia	**STUDY SHOULD ONLY CONSIDER SELF-REPORTED HEALTHY SUBJECTS** **Any type of smoking-associated disease (cancer, cardiovascular, and respiratory)** **Renal dysfunction** **Bronchitis** **Asthma** **Hyperlipidemia – TRICKER** **Individuals with the following diseases to be excluded:** • **Cancer – All** • **CHD** • **Hypertension** • **Stroke** • **Heart infarction** • **Bronchitis** • **Emphysema** • **Asthma** • **Hyperlipidemia - SANDERS**	**Renal dysfunction (unknown influence on creatinine and urinary biomarkers).** **Bronchitis indication for developing respiratory disease. Asthmatics don't usually smoke.** **Hyperlipidemia (HDL/LDL ratio). – TRICKER** **Can we base exclusion on current activity levels/"health" of the individuals rather than existence of disease state? A diabetic may be very healthy if he/she responds well to medication, eats properly and exercises regularly. This is also true for people who have had stroke or heart attacks, asthmatics, etc. – KINSER** **It is almost universal in epidemiological studies of both ETS exposure and active smoking to exclude all individuals with potential smoking diseases. In this case, it is probably worthwhile being even more restrictive, in that subjects with certain diseases, even if they continue to smoke, could well change the manner in which they smoke. - SANDERS**
8a [von Holt, Sanders]	Should the health status of the subjects be verified for exclusions? • EKG • X-ray • Routine hematology • Pulm. function	**NO CLINICAL DIAGNOSIS OR DIAGNOSTIC HEALTH CHECK, except for routine hematology. - TRICKER**	**Use questionnaire to ask questions about heath status and exclude the above health conditions. Inclusion of clinical or diagnostic tests introduces additional ethical constraints and requirement to notify subjects of adverse findings. Difficult to define in-/exclusion criteria for ECG.** **Routine hematology should be performed to obtain cholesterol and HDL/LDL status. Routine hematology does not include HIV and hepatitis testing (might be required by CRO if analyzing blood samples). - TRICKER**

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DESIGN REFINEMENTS

CONS. NUMBER	QUESTION	RECOMMENDATION	COMMENT
9 [Tricker, Haussmann]	What kinds of analyses are considered for the stored sample materials?		Exclusion of diagnostic testing significantly increases study population; insurance issues
10 [Carmines, Elves]	Can the clinical laboratory tests be undertaken under clinical standards instead of GLP?	GLP required 'if available', but clinical standards required **Yes, In cases where clinical standards are not available, GLP may be substituted. - ELVES**	Clinical labs are not GLP certified; clinical standards as required for clinical trials **FDA GCP regulations mandate that all laboratories be accredited or licensed under clinical standards (i.e. CLIA). Some laboratories may have in addition to clinical licensing, GLP. In this case the additional accreditation should be noted - ELVES**
11 [Carmines, Elves]	Do the biomarkers of exposure require GLP certified labs?	GLP required 'if available', but clinical standards required	**FDA approved studies require that labs meet clinical standards. - ELVES**
12 [von Holt]	Do we require external QA inspections?	Yes, esp. if GLP will not be required for biomarkers and clinical laboratory tests	QA criteria should be defined beforehand. **Determine what the GLP practices of the CRO options and their affiliated laboratories are. - LEYDEN**
13 [Sanders, Haussmann, Roemer]	Definition of current smoker	At least 6 months more than 4 cig. /day. **Regular smoking of at least one cigarette per day of a reported brand for at least one year. – TRICKER**	Based on 7 x half-life of NNAL
14 [Kinser, Leyden, all]	Any definition/restrictions for the smoking activity prior to sample collection	No, sample collection within 10 min. after admission in the research facility	**No restrictions, but require a record of last 2 or 3 days – KINSER** **Attempt to collect serum samples the same time interval following the last cigarette. In any case, obtain the information on time interval since the last cigarette. - LEYDEN**

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DESIGN REFINEMENTS

CONS. NUMBER	QUESTION	RECOMMENDATION	COMMENT
15 [Leyden, Rustemeier]	Method of exhalate collection?	**Air sampling for carbon monoxide in expired air; sampling in impermeable plastic bags (e.g., Tedlar bags or similar) after discarding the dead space (Jarvis, M.J., Et al., 1980) is the most frequently used and most convenient procedure.** **Air sampling for acetonitrile in expired air: Breath for the determination of acetonitrile with PTR-MS (Jordan, A., et al., 1995; Prazeller, P. et al., 1998) may also be collected in Tedlar bags. The stability of this gas samples, however has to be checked. – von Holt**	**This can only be specified by the CRO (based on availability of instrumentation) – TRICKER** **The only viable method is the use of commercial exhalate bags. The CRO should be knowledgeable about these. There are a few brands with various design features. These bags are not readily transportable in large numbers, so the analytical tool needs to be at the clinical site if possible. - LEYDEN**
16 [Haussmann , Tricker]	What analyses with the induced sputum?	**None recommended at present. Banking of sputum samples. - TRICKER**	
17 [Kinser]	Method for acetonitrile determination?	**References method (Lindinger et al., Int. J. Mass Spectrometry Ion Processes, 173, 191-241, 1998). - TRICKER**	**This can only be specified by the CRO (based on availability of instrumentation) – TRICKER** **It will be necessary to have a method for acetonitrile and CO that can use the same bag sample. Or, that we use a separate method for CO that does not involve a bag. - LEYDEN**
18 [Leyden, Kinser]	Method of CO determination in exhalate?	Use of instruments used by pulmonologist in their clinics **Standardized method (e.g., sample collection in Tedlar bag and analysis in one laboratory). - TRICKER**	Specifications required to ensure sensitivity and comparability among different collection sites
19 [Nelson, Jones]	Definition of demographics for smokers and non-smokers: • Age distribution • Male/female • Ethnic distribution • Socioeconomic distribution • Diet (for non-smokers)	• Age distribution • Male/female • Ethnic distribution • socioeconomic	Being addressed with the exception of data on diet. – NELSON **One cannot define evenly distributed demographics for a factor that applies only to non-smokers. It might be most difficult to arrive at an even distribution for diet. – SANDERS**

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DESIGN REFINEMENTS

CONS. NUMBER	QUESTION	RECOMMENDATION	COMMENT
20 [all, Sanders, Jones]	Should demographics distribution be representative for total population or each of the 4 tar sections?	Total population	An attempt should be made particularly in the pilot study to identify persons in each of the 4 sections. By doing this in the pilot study, we will identify any problems in obtaining subjects for any of the sections. It may be that as a result of what is learned in the pilot section, improvements can be made for the larger study. On the other hand, we may learn that it is going to be impossible to have each of the tar sections represent the total population. This will then be documented in the pilot – NELSON Based on a population size of 300 subjects per group it is probably impossible to have a representative demographic distribution in each group. – TRICKER That will mean this is not a compensation study. – KINSER **Both age distribution and gender should be matched as closely as possible for the four tar groups and the control. Socioeconomic distribution is almost as important. Ethnic distribution is less important. To accomplish this, one must obtain a larger sample than the actual sample used. – SANDERS**

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DESIGN REFINEMENTS

CONS. NUMBER	QUESTION	RECOMMENDATION	COMMENT
21 [all]	Should the pilot study divide tar groups into 2 consumption groups (e.g. 1. up to 12 cig./day; 2. >= 13 cig./day)	**No – KINSER**	No - Stratification may also result in having small numbers in cells which limits or impedes analysis – NELSON It might be a useful way to analyze the data. – KINSER **Each sample should be treated homogeneously. However, information on number of cigarettes smoked per day should be collected. This factor should then be taken into account in the preliminary data analysis. - SANDERS**
22 [Kinser, Leyden, Schepers]	Should the pilot study collect sequential urine samples for each participant?	Yes	
23 [all]	Should non-filter cigarettes be excluded from the study?	No **Yes, in pilot study - ELVES**	Small market segment and study is designed to NOT discriminate between different cigarette designs. **In the pilot, adding non-filter cigarettes adds an additional variable and uncertainty that can not be accurately addressed given the small number of subjects. – ELVES** **Upper limit on the highest tar group (20-mg tar) will eliminate most non-filter cigarettes. -** SANDERS

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